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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,545	12/17/2003	Masahiro Kawaguchi	03500.017338	6817

5514 7590 06/13/2008

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EXAMINER	
LIU, SUE XU	
ART UNIT	PAPER NUMBER
1639	
MAIL DATE	DELIVERY MODE
06/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/736,545	KAWAGUCHI ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,6,7 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 6, 7 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 1, 3-5, and 8-27 have been canceled as filed on 9/10/07.

Claims 2, 6, 7 and 28-30 are currently pending.

Claims 2, 6, 7 and 28-30 are being examined in this application.

Election/Restrictions

2. Applicant's election of Group II (Claims 2-7) in the reply entered on 11/14/2005 is as previously acknowledged.

3. Applicants also elected the following species as previously acknowledged:

A.) fluorescent markers;

B.) two kinds of external standard probes;

C.) one kind of internal standard probes;

D.) single-stranded DNA;

E.) 20 residues each of internal and external probes;

F.) two sets of primers that will produce 500 bp and 200 bp products;

G.) a "microorganism"' is selected as the most specific species explicitly recited in the specification;

H.) one nucleic acid;

I.) two.

Priority

4. This application appears to be a CONTINUATION of PCT/JP03/07918 filed on 6/23/03.

Receipt is acknowledged of the following papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file:

A.) An application filed in JAPAN (2002-191390) on 6/28/2002.

B.) An application filed in JAPAN (2002-183249) on 6/24/2002.

Claim Objection(s) / Rejection(s) Withdrawn

5. In light of the Abandonment of the co-pending application, 09/951,972, the following ODP rejection is withdrawn:

Claims 1 and 6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 224, 226, 227 and 242 of copending Application No. 09/951,972 (US 20020146715; hereinafter referred to as the '972 application).

6. In light of applicants' amendments to the claims, the following claim rejection is withdrawn:

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections Maintained

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(Note: the instant claim numbers are in bold font.)

Delenstarr et al

8. Claims 2, 6, 7, and 28-30 are rejected under 35 U.S.C. **102(b)** as being anticipated by Delenstarr et al (US PGPUB 2002/0051973 A1; May 2, 2002; cited previously). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

The instant claims briefly recite "a DNA micro-array *for detecting nucleic acid molecules having target base sequences in a sample where the existence/non-existence or amount of said nucleic acid molecules having the target base sequences is unknown*, said array comprising:

a substrate; and

nucleic acid probes including base sequences complementary to the target base sequences, the nucleic acid probes being immobilized on the substrate,

wherein the array contains at least two probes *for an internal standard nucleic acid added at a known amount to the sample at the time of PCR amplification of said nucleic acid molecules*

having the target base sequences, said at least two probes having different sequences from each other and having sequences complementary to the internal standard nucleic acid,

wherein said at least two probes are available *for quantitative evaluation of PCR of said nucleic acid molecules having the target base sequences*, and

wherein said at least two probes include at least two probes *corresponding to PCR products with different chain lengths derived from the internal standard nucleic acid.*

The instant claim 2 (the independent claim) recites a product of a DNA microarray comprising the following structural elements: a substrate, nucleic acid probes immobilized on the substrate complementary to target base sequences, and at least two nucleic acid probes immobilized on the substrate complementary to "an internal standard nucleic acid", as indicated by the underlined region in the above claim citation.

The above claim recitations in *Italic* such as "quantitative evaluation of PCR" and "*for an internal standard nucleic acid added at a known amount to the sample at the time of PCR amplification of said nucleic acid molecules having the target base sequences"* are intended uses for the claimed product of a DNA microarray. For example, the newly added recitation, "*for an internal standard nucleic acid added at a known amount to the sample at the time of PCR amplification of said nucleic acid molecules having the target base sequences*", appears to recite a method step and does not provide additional structural limitation to the claimed product of a microarray, or more specifically, to the "at least two probes".

In addition, the specification of the instant application discloses the internal standard probe as "a probe for detecting an internal standard nucleic acid to be used to assist quantitative

determination of a target nucleic acid," and the internal standard nucleic acid as "a nucleic acid of a known base sequence" (page 12 of the specification). Therefore, the internal standards and probes could be interpreted, for example, to be any nucleic acid sequences that are known. As long as at least two probes are complementary to at least one nucleic acid (i.e. the "internal standard nucleic acid" in a sample, the instant clamed structural limitation of at least two probes is met.

Further, the newly added recitation, "*where the existence/non-existence or amount of said nucleic acid molecules having the target base sequences is unknown"* is also a recitation of intended use for the instant claimed microarray. The said recitation is only relevant to the "sample" for which the instant claimed microarray is intended to be used, and thus does not add additional structural limitation of the instant claimed microarray or its immobilized probes.

Delenstarr et al, throughout the publication, teach a set of features comprising oligophophodiester probes (reads on microarrays of **clm 2**; Claim 1 of the reference). The reference teaches hybridization features comprising hybridization probes (bound to a surface; Claim 2 of the reference) that selectively hybridize to a detectably labeled target nucleotide sequence (reads on the probes for the target nucleic acid of **clm 2** as well as probes of **clm 30**; Claim 1 of the reference). The reference also teaches background features comprising background probes (as listed in Claim 4 of the reference) that do not selectively hybridize to said nucleotide sequence (read on the probes of **clm 30**; Claims 2 and 4 of the reference). In addition, the reference teaches the features (or array) comprising target probes, test-background probes

(read on either internal probes of **clm 2**), and standard-background probes (read on internal probes of **clm 2**); (See Claim 30 of the reference).

The reference also teaches arrays comprising multiple probes that hybridize to different portion of a single gene (or the cRNA of a single gene) (e.g. p. 12+). For example, the reference teaches various probes (with different sequences) that are complementary to the P53 gene (e.g. pp.12-13; Table 1). That is the P53 gene (or the PCR product of the P53) is the "internal standard" included in the "sample, and the different probes (such as the ones listed in Table 1) are the "at least probes" that "having different sequences from each other and having sequences complementary to the internal standard nucleic acid" as recited in **clm 2**.

The reference also teaches the probes could be 25 bases long (such as SEQ ID NO 5 as recited in Claim 5, for example), which reads on the length recited in **clm 7**. Furthermore, the reference recites various different probes with different sequences (such as the one directed in Claim 5 of the reference), which have the functions of hybridizing to PCR products with different chain lengths. The reference further teaches that the probes can be synthesized (See paragraph [0104] of the reference), which reads on limitation of **clm 6**. The reference also teaches the concentration of different probes on the microarray (e.g. Example 6, p. 15+; especially p.11), which reads on the spots having the same or different concentrations of **clms 28 and 29**.

Furthermore, the reference also teaches probes that do not hybridize to any nucleic acid molecules in the sample as indicated by the dim spots (which probes were not hybridized to any sample nucleic acids) on the array (see, for example, Figures 3 and 7), which reads on the "does not hybridize" recitation of **clm 30**.

The probes (or "internal probes") taught by the reference also reads on the inherent property of "corresponding to PCR products with different chain lengths" as recited in **clm 2**, because the probes can hybridize to target molecules with different chain lengths. For example, a probe on the array with 20 nucleotides complement to a target molecule with 30 nucleotide length (comprising the 20 nucleotide complement to the probe) would also be complement to a target molecule with 40 nucleotide length (comprising the same 20 nucleotide complement to the probe). In other words, the recitation "corresponding to PCR products with different chain lengths" does not offer any additional structural limitation to the claimed probes.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the reference does not teach every element of the claimed invention. (Reply, p. 5). Applicants specifically assert that the reference does not teach the "intended use" recitations. (Reply, pp.5-6)

Applicants are respectfully directed to the above rejection for detailed discussion on how the cited reference teaches each and every element of the instant claimed invention.

In response to applicant's argument that the reference does not teach the feature, (i)" *where the existence/non-existence or amount of said nucleic acid molecules having the target base sequences is unknown"; (ii) "for an internal standard nucleic acid added at a known amount to the sample at the time of PCR amplification of said nucleic acid molecules having the target base sequences*; (iii) "*for quantitative evaluation of PCR of said nucleic acid molecules*

having the target base sequences", a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In the instant case, the above said claim recitations are intended use for the claimed product of a DNA microarray. The feature "internal standard nucleic acids" is not a structural part of the claimed array, but it is a part of the "sample" for which the claimed array can act upon. Similarly, the "PCR amplification" recitation is reciting a method step, which does not result in a structural difference to the instant claimed array. That is the recitation of "the internal standard nucleic acids are added at a known amount to the sample at the time of PCR amplification…" only recite a method step and does not provide additional structural limitation to the claimed product of a microarray. Thus, the microarray of the reference is structurally the same as the instantly claimed microarray, and is capable of performing the recited intended uses without evidence to the contrary.

Applicants also assert the reference does not teach "at least two probes have different sequences from each other and have sequences complementary to the internal standard nucleic acid". (Reply, p.4, para 5).

Applicants are respectfully directed to the above discussion on reference's teaching on "at least two probes" for the internal standard nucleic acid.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

'103

11. Claims 1, 6 and 7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 6, 11, and 12 of U.S. Patent No. 6,924,103 (8/2/2005). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed invention in the '103 patent read on or is obvious over the instant claimed invention. The previous rejection is maintained for the reasons of record.

'420

12. Claims 1 and 6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 52 and 5-7 of copending Application No. 09/764,420 (US 20030198952; hereinafter referred to as the '420 application). Although the

conflicting claims are not identical, they are not patentably distinct from each other because the claimed invention in the '420 application read on or is obvious over the instant claimed invention. The claims of the '420 are relied upon as filed on 10/31/07, which are the current pending claims as of the date of the instant office action. The previous rejection is maintained for the reasons of record.

Discussion and Answer to Argument

13. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants state "Applicants will consider the possibility of filing a Terminal Disclaimer" to overcome the ODP rejection over the '103 patent (Reply, p.7).

However, a Terminal disclaimer is not filed as of the date of instant office action. Thus, the above ODP rejection over the '103 patent is maintained for the reasons of record.

Applicants also state "a provisional double patenting rejection should be withdrawn… if the provisional double patenting rejection is the only rejection remaining in an application" to traverse the rejection over the '420 application (Reply, p.7).

However, the said provisional double patenting rejection is not the only remaining rejection in the instant application. Thus, the said ODP rejection is maintained for the reasons of record.

New Claim Rejections

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter Rejection

15. Claims 2, 6, 7 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is necessitated by applicants' amendments to the claims.

Claim 2 has been amended as part of the claim amendment filed on 2/29/08. However, the instant specification does not provide support for the claimed array recited in Claim 2. In particular, the instant specification and claims as originally filed do not disclose a DNA microarray comprising "at least two probes" "for **an** internal standard nucleic acid" "having different sequence for each other and having sequences complementary to the internal standard nucleic acid" (emphasis added). That is the original disclosure does not appear to provide support for the at least probes for one single internal standard nucleic acid, as well as the at least two probes having different sequences and yet complementary to the said internal standard nucleic acid.

If Applicant believes this rejection is in error, applicant must disclose where in the specification support for the entire scope of the amendment(s) and/or new claims can be found. As a result, Claim 2 and its dependent claims represent new matter.

Second paragraph of 35 U.S.C. 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 2, 6, 7 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by applicants' amendments to the claims.

Claim 2 recites the limitation "the time of PCR amplification" in line 9. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Dudley et al

20. Claims 2, 6, 7 and 28-30 are rejected under 35 U.S.C. **103(a)** as being unpatentable over Dudley et al (PNAS. Vol. 99: 7554-7559. May 28, 2002 (cited previously) and the accompanying "Supplementary Material" downloaded from //arep.med.Harvard.edu/masliner/supplement.htm). The rejection is necessitated by applicant's amendment to the claims. This rejection is necessitated by applicants' amendments to the claims.

The instant claims briefly recite "a DNA micro-array *for detecting nucleic acid molecules having target base sequences in a sample where the existence/non-existence or amount of said nucleic acid molecules having the target base sequences is unknown*, said array comprising:

a substrate; and

nucleic acid probes including base sequences complementary to the target base sequences, the nucleic acid probes being immobilized on the substrate,

wherein the array contains at least two probes *for an internal standard nucleic acid added at a known amount to the sample at the time of PCR amplification of said nucleic acid molecules having the target base sequences*, said at least two probes having different sequences from each other and having sequences complementary to the internal standard nucleic acid,

wherein said at least two probes are available *for quantitative evaluation of PCR of said nucleic acid molecules having the target base sequences*, and

wherein said at least two probes include at least two probes *corresponding to PCR products with different chain lengths derived from the internal standard nucleic acid.*

The instant claim 2 (the independent claim) recites a product of a DNA microarray comprising the following structural elements: a substrate, nucleic acid probes immobilized on the substrate complementary to target base sequences, and at least two nucleic acid probes immobilized on the substrate complementary to "an internal standard nucleic acid", as indicated by the underlined region in the above claim citation.

The above claim recitations in *Italic* such as "quantitative evaluation of PCR" and "*for an internal standard nucleic acid added at a known amount to the sample at the time of PCR amplification of said nucleic acid molecules having the target base sequences"* are intended uses for the claimed product of a DNA microarray. For example, the newly added recitation, "*for an internal standard nucleic acid added at a known amount to the sample at the time of PCR amplification of said nucleic acid molecules having the target base sequences*", appears to recite a method step and does not provide additional structural limitation to the claimed product of a microarray, or more specifically, to the "at least two probes".

In addition, the specification of the instant application discloses the internal standard probe as "a probe for detecting an internal standard nucleic acid to be used to assist quantitative determination of a target nucleic acid," and the internal standard nucleic acid as "a nucleic acid of a known base sequence" (page 12 of the specification). Therefore, the internal standards and probes could be interpreted, for example, to be any nucleic acid sequences that are known. As long as at least two probes are complementary to at least one nucleic acid (i.e. the "internal

standard nucleic acid" in a sample, the instant clamed structural limitation of at least two probes is met.

Further, the newly added recitation, "*where the existence/non-existence or amount of said nucleic acid molecules having the target base sequences is unknown*" is also a recitation of intended use for the instant claimed microarray. The said recitation is only relevant to the "sample" for which the instant claimed microarray is intended to be used, and thus does not add additional structural limitation of the instant claimed microarray or its immobilized probes.

Dudley et al, throughout the publication, teach measuring absolute expression with microarrays with a calibrated reference sample, and generating ratios between sample intensities and intensities of the oligo reference measure sample RNA levels (See Abstract of the reference). The reference teaches microarrays comprising probes generated from yeast ORF PCR product set, and an oligo reference sample with certain nucleic acid sequence (See page 7554, right column, 4th paragraph of the reference). The yeast ORF PCR product set contains over 6,000 yeast ORF (see the "Supplementary Material" (p. 9 of Supp.) described on p. 7555, left column, last paragraph of the reference), which could contain the "target nucleic acid" (could be any yeast gene of interest from the >6,000 ORF PCR products). The oligo reference sample could be the "internal" probes for the internal standards since the oligo sequence is known and contained on the microarray. In addition, any other probes for the >6,000 genes that is not considered to be the gene of interest (the target gene) and is not complementary to the target gene sequence could be considered as the internal probes. For example, the RPL29, or the PHO88 genes listed in Figure 3 on Page 7557. The probes for these genes on the microarray would hybridize to genes

with different PCR products (different lengths). The reference further teaches that the microarray are generated either by printing PCR generated cDNA or commercially available oligo sets (See Supplemental Web Site as described on Page 7555, left column, last paragraph of the reference; see also the Supplementary Figure 4), which read on the various nucleic acid probes immobilized on the substrate, and different sequences placed at different positions of **clm 2** as well as the "more than one probe" of **clm 30**. In addition, the reference teaches the oligo reference sample is 20 bases long (page 7554, right column, 4th paragraph of the reference), which would refer to nucleic acid has a chain length of 15 to 75 bases, as recited in **clm 7**. The reference further teaches the Yeast Genome Oligo Set were printed at a concentration of 10 pmols/ml in 150 mM potassium phosphate (See Supplemental Web Site as described on Page 7555, left column, last paragraph of the reference), which reads on probes with the same concentration of **clm 29**. The reference also teaches that the microarray are generated either by printing PCR generated cDNA or commercially available oligo sets (See Supplemental Web Site as described on p. 7555, left column, last paragraph of the reference), which reads on the synthetic nucleic acids immobilized on the substrate as recited in **clm 6**. The reference also teaches resuspending the various PCR products in 150 mM potassium phosphate before immobilized on the substrate (Supplemental Material, p. 9), which reads on "spots having different concentrations" of **clm 28**.

The probes (or "internal probes") taught by the reference also reads on the inherent property of "corresponding to PCR products with different chain lengths" as recited in **clm 2** and **clm 30**, because the probes can hybridize to target molecules with different chain lengths. For example, a probe on the array with 20 nucleotides complement to a target molecule with 30

nucleotide length (comprising the 20 nucleotide complement to the probe) would also be complement to a target molecule with 40 nucleotide length (comprising the same 20 nucleotide complement to the probe).

Furthermore, the reference also teaches probes that do not hybridize to any nucleic acid molecules in the sample as indicated by the dim spots (which probes were not hybridized to any sample nucleic acids) on the array (see, for example, Supplement, Figures 3 and 4), which reads on the "does not hybridize" recitation of **clm 30**.

Although the Dudley reference does not explicitly teach "at least two probes" having different sequences from each other and having sequences complementary to the internal standard nucleic acid" as recited in **clm 2**, it is prima facie obvious for one of ordinary skill in the art to include more than one probes that is complementary to one sample nucleic acid (or "an internal standard nucleic acids".

A person of ordinary skill in the art would have been motivated at the time of the invention to include additional probes that are complementary to different portion of a sample nucleic acid, because the different probes can provide cumulative hybridization signals to detect the said sample nucleic acid (such as an internal standard nucleic acid). It would have been obvious to one of ordinary skill in the art to use the additional complementary probes (such as additional oligonucleotide probes) as taught by Dudley to increase detection accuracy in a microarray hybridization assay, as using the known techniques (including generating microarray probes that are complementary to a sample nucleic acid) are within a person of ordinary skill's technical grasp.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Dudley et al have demonstrated generating DNA microarray with various probes having various sequences.

Discussion and Answer to Argument

21. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants are respectfully directed to the above rejection for detailed discussion on how the cited reference renders the instant claimed invention obvious.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sue Liu/
Patent Examiner, AU 1639
5/28/07

/Jon D. Epperson/
Primary Examiner, AU 1639